REMARKS

In response to Office Action mailed on May 22, 2007, please consider the following remarks. The amended claims are drawn to a method of alleviating a symptom of dry eye syndrome by administering to a subject suffering from or at risk of developing dry eye a composition containing a carotenoid and a polyphenol and co-administering to the subject a composition comprising an omega-3 fatty acid.

Due to a clerical error, a Notice of Appeal was filed on September 5, 2007 in the present case. The erroneous Notice of Appeal referenced the serial number of the present application (USSN 10/621,802) in the header of the transmittal papers but stated that it was in response to a Final Office Action mailed on March 5, 2007 (which was the status of the parent case (USSN 10/345,856)). Applicants therefore request that the Patent Office vacate the Notice of Appeal in this case and enter this amendment.

Claims 68-83 and 107-113 are pending. The claims have been amended for clarity. No new matter has been added by this amendment.

35 U.S.C. 112, second paragraph

Claims 107-113 were rejected for indefiniteness of the phrase "wherein the composition comprising a carotenoid and a polyphenol comprises" The Examiner stated that some of the ingredients listed are neither a carotenoid nor a polyphenol. The composition of claims 108 to 113 includes ingredients in addition to a carotenoid and a polyphenol. Claims 108 to 113 have been amended for clarity by deleting the phrase "comprising a carotenoid and a polyphenol". Therefore, this rejection should be withdrawn.

35 U.S.C. 112, first paragraph

Claims 68-83 and 107-113 were rejected for failing to comply with the written description requirement. In support of this ground of rejection, the Examiner states:

> The claims are directed to a method of treating "a symptom of dry eye syndrome". Such method requires treatment of unspecified disease and no evidence indicates that treatable disease was known to applicant. Therefore, the fact pattern indicates that applicant was not in possession of the claimed method of use. In the absence of understanding the disease to be treated, the artisan would not have accepted that applicant was in possession of the invention.

Applicants traverse. The Examiner's position is not understood. The originally-filed specification is replete with description of dry eye syndrome, methods of identifying dry eye syndrome, and methods of treating dry eye syndrome. For example, the background of the invention states:

> Aqueous tear-deficient dry eye syndrome is a disruption of the ocular surface-lacrimal gland homeostatic cycle. It is characterized by dry inflammation of the lacrimal gland, and presence of a dense infiltrate of inflammatory cells in and around the tear duct causing high localized expression of pro-inflammatory cytokines. (page 1, lines 10-13, of the specification).

Text spanning page 17-18 of the specification provides further evidence of the in-depth understanding of the disorder possessed by the inventors at the time of the invention:

> Dry eye syndrome is one of the most common problems treated by eye physicians. Over ten million Americans suffer from dry eyes. It is usually caused by a problem with the quality of the tear film that lubricates the eyes. Dry eye syndrome has many causes. One of the most common reasons for dryness is simply the normal aging process. As we grow older, our bodies produce less oil – 60% less at age 65 then at age 18. This is more pronounced in women, who tend to have drier skin then men. The oil deficiency also affects the tear film. Without as much oil to seal the watery layer, the tear film evaporates much faster, leaving dry areas on the cornea. Other factors, such as hot, dry or windy climates, high altitudes, air-conditioning and cigarette smoke also cause dry eyes. Contact lens

> wearers also suffer from dryness because the contacts absorb the tear film, causing proteins to form on the surface of the lens. Certain medications, thyroid conditions, vitamin A deficiency, and diseases such as Parkinson's and Sjogren's also cause dryness. Women frequently experience problems with dry eyes as they enter menopause because of hormonal changes.
>
> Symptoms of dry eye include itching, burning irritation, redness, blurred vision that improves with blinking, excessive tearing, increased discomfort after periods of reading, watching TV, or working on a computer.
> There are several methods to test for dry eyes. For example, the underlying cause of the dry eyes will be determined by measuring the production evaporation rate and quality of the tear film. Special drops that highlight problems that would be otherwise invisible are particularly helpful to diagnose the presence and extent of the dryness.

Additional characterization of the symptoms and underlying causes of dry eye syndrome appear throughout the specification, e.g., at page 20, lines 8-11.

> Ocular inflammation in dry eye occurs in part due to breach of the blood-ocular barrier and the attraction of macrophages, PMNs and other leukocytes to affected tissue. This process is mediated substantially by release of inflammatory metabolites such as prostaglandins both from ocular tissue and from emigrant leukocytes.

Moreover, Applicants call the Examiner's attention to a textbook entitled Principles and Practice of Ophthamology (Albert et al., 2000, Principles and Practice of Ophthamology, 2nd ed., W.B. Saunders Co., pp. 982-1001; provided as Appendix A) devotes a chapter to "Dry-Eye Disorders" and cites back to references dating back to 1940 describing dry eye syndrome.

The specification provides comprehensive disclosure regarding dry eye syndrome as a medical condition. This disclosure coupled with the extensive disclosure of exemplary formulations to be administered for treatment of the syndrome are unequivocal evidence that the inventors were in possession of the inventive methods of

alleviating a symptom of this very well characterized condition. This ground of rejection simply without merit and should be withdrawn.

Next, the Examiner calls into question whether the claim terms "carotenoid", "polyphenol", and "omega-3 fatty acid" meet the written description description requirement of § 112 citing to case law as well as the Written Description Guidelines ("Guidelines") 66 Fed. Reg. 1099 (Jan. 5, 2001). At the top of page 4 of the Office Action, the Examiner states:

> Applying the reasoning of the above-cited case law to the facts at hand, the instant specification fails to provide an adequate written description of suitable carotenoids, polyphenol compounds and omega-3 fatty acids. The specification describes only a limited number of such compounds. The instant claims generally recite "a carotenoid", "a polyphenol" and "an omega-3 fatty acid". When functional claims are drawn this broadly, they are inclusive of any carotenoid, any polyphenol and any omega-3 fatty acids. Accordingly, the instant specification fails to provide an adequate written description of "a carotenoid", "a polyphenol" and "an omega-3 fatty acid" generally.

Description of "only a limited number of such compounds" does not destroy written description. The specification need not provide an exhaustive list of examples in order to fulfill the written description requirement. To satisfy the written description requirement, an Applicant must convey with reasonable clarity to those skilled in the art as of the filing date that he or she was in possession of the invention as claimed, i.e., does the disclosure reasonably convey to the artisan that the inventor has possession of the invention as claimed (MPEP at 2163.02). The test of whether the written description is met for a genus claim is to determine whether a representative number of species have been described.

With regard to the claim term "carotenoid", the specification discloses astaxanthin, zeaxanthin, beta-carotene, and mixed carotenoids (page 1, line 24, of the specification.) Additional disclosure pertaining to carotenoids such as the lipid-soluble astaxanthin (3,3'-dihydroxy-4,4'-diketo-ß-carotene) as well as other carotenoid compounds is provided on page 6, lines 12-29, and page 7, line 7, of the specification. Dependent claim 68 specifically recites astaxanthin, zeaxanthin, and mixed carotenoids. The specification teaches that the structure is similar to that of the well-known carotenoid, beta-carotene, and have the biological properties: free radical scavenging activity, antioxidant properties, and the ability to protect against lipid peroxidation and oxidative damage of LDL-cholesterol in cell membranes, cells, and tissues. In view of the description of a representative number of species by chemical name, formula, and function, Applicants request that this rejection be withdrawn.

"Polyphenols" are well known as a group chemical compositions found in plants that are characterized by the presence of more than one phenol group per molecule. The specification discloses numerous examples of a polyphenol, e.g., curcuma longa root powder, green tea, grape seed extract, a citrus bioflavonoid, or a cox-2 inhibitor such as a quercetin, a bilberry extract, a hops PE, blueberry powder or tart cherry powder (claimed in dependent claims such as claims 75-77). The specification further teaches that the polyphenols be anti-inflammatory. Applicants submit that the specification describes a representative number of species so as to show that Applicants were in possession of the claimed genus in fulfillment of the written description requirement.

The "omega-3 fatty acid" class of compounds is also well known in the art. Two examples of this well known class of fatty acids are literally disclosed in the specification by their chemical name: eicosapentaenoic acid and docosahexaenoic acid (page 2, line 12, of the specification). Dependent claims such as claim 73 specifically require that the omega-3 fatty acid is eicosapentaenoic acid or docosahexaenoic acid. Given that this is a relatively small and well-defined class of fatty acids defined by their structure, i.e., they have a double bond in the omega-3 position, Applicants submit that specific description of two members of the class constitutes a representative number of species to recognize from the disclosure that Applicants were in possession of the claimed invention.

CONCLUSION

Applicants believe that the application and claims are in condition for allowance. The Examiner is invited to contact the undersigned at the number or email listed below should she believe that there are any remaining issues that could be more easily resolved by personal or telephonic interview.

With a three-month extension of time, these documents are due on or before November 22, 2007. Applicants submit herewith a Petition for a Three-Month Extension of Time, along with a check for the fee of $525.00. The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 21534-002CIP.

Respectfully submitted,

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Principles and **Practice** of **Ophthalmology**

SECOND EDITION

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CHAPTER 74

Dry-Eye Disorders

Jeffrey P. Gilbard

Over 50 years ago Henrik Sjögren described a disease characterized by autoimmune damage to lacrimal gland tissue, decreased tear secretion, and ocular surface disease, and he called the disease *keratoconjunctivitis sicca* (KCS).[1] It is now recognized that KCS, or "dry eye," refers to, or is a component of, a variety of disorders. It is characterized by the ocular surface disease that results from any condition or circumstance that decreases tear secretion or increases tear film evaporation sufficient to result in loss of water from the tear film. There has been tremendous growth in our understanding of these diseases, improving our ability to diagnose and treat these patients who for years have tested the limits of our diagnostic acumen and therapeutic abilities.

Anatomy and Physiology of the Tear Film

The maintenance of a normal tear film depends on the maintenance of a normal ocular surface (i.e., a normal epithelial surface and a normal mucous layer produced by this surface). Similarly, the ocular surface cannot retain its normal structure in the absence of a normal tear film. For these reasons, the division between the eye and the tear film is really an artificial one, and descriptions of the tear film should begin with the ocular surface.

OCULAR SURFACE

In one sense the tear film begins in fluid reservoirs beneath the ocular surface. Mishima was the first to recognize the contribution of the aqueous humor to the aqueous component of the tear film.[2] The hydrostatic pressure exerted by the aqueous and the osmotic gradient that develops across the cornea as a result of tear evaporation cause a continuous flow of water from the aqueous side of the cornea to the tear side. Mishima estimated this flow to equal 3 $\mu L/cm^2/hr$ in rabbits. In the conjunctiva, where the blood vessels are fenestrated,[3] Maurice postulated that fluid moves across the conjunctival epithelium into the tear film in response to the instillation of hypertonic drops.[4] It seems likely that some such fluid movement could take place based on the osmotic gradient between serum and tears. Janssen and van Bijsterveld presented evidence for the leakage of serum proteins across the conjunctival epithelium into the tears.[5]

Fundamental to the wetting of the ocular surface is the nature of the epithelial cell membrane. In humans, the superficial cell membranes of the cornea and conjunctiva are packed densely with microplicae and microvilli, and these surface structures probably play a role in the retention of an evenly distributed mucous layer. Dilly and Mackie have shown that located within conjunctival epithelium are membrane-bound subsurface vesicles that contain glycoproteins.[6] These vesicles apparently rise to the tear-side surface of the cell and then open and fuse with the cell membrane. In this manner, these vesicles appear to distribute their glycoprotein throughout the epithelial cell surface, contributing to the glycocalyx.

MUCOUS LAYER

The mucous layer overlying the glycocalyx is secreted by the goblet cells. Conjunctival goblet cells are distributed throughout the bulbar and palpebral conjunctiva, with some goblet cells secreting their mucus directly onto the ocular surface and others secreting their mucus into crypts that rise to the ocular surface.[7] Mucus has very high lubricity, and one major function of the goblet cells and the mucus that they produce is to provide lubrication for the ocular surface. Another major function, as we shall see, is to trap foreign matter and eliminate it from the eye.

Kessing studied the distribution of these goblet cells throughout the conjunctiva in humans and reported that these cells are denser nasally than temporally.[8] Holly and Lemp estimated that the adsorbed precorneal mucous layer is between 0.02 and 0.04 μm thick and that the superficial layer of dilute mucin is about 4 μm thick.[9] Nichols and coworkers, using transmission electron microscopy fixation techniques that preserve the mucous layer during fixation, showed that the mucous layer overlying the cornea measures between 0.6 and 1.0 μm thick, whereas the layer overlying the conjunctiva measures 2 μm to as much as 7 μm thick in certain regions.[10] The mucus was in continuity with the cell membrane glycocalyx, providing support for the hypothesis that the glycocalyx binds the overlying mucus. It may be impossible to define the precise thickness of the mucous layer because the surface mucus is hydrated, and the transition between the mucous layer and the aqueous layer is probably a gradual one.

Interestingly, the mucous layer is thicker over the conjunctiva than over the cornea. Adams has studied both the morphology of the mucous layer and the action of the mucous layer in removing foreign material from the tear film.[11] Mucus exists on the ocular surface in a structureless continuum, in granules arranged in clusters or sheets, and as fine strands. Foreign particles are captured in these fine networks of conjunctival mucus that collapse and migrate toward the medial canthus progressively with each blink. During this migration no mucus networks are observed in the precorneal

tear film, and mucus with trapped debris is expelled from the eye at the medial canthus.

More is now known about the regulation of mucus secretion by goblet cells. It appears that when the electrolyte composition of the adjacent fluid differs from that of normal tear fluid,[12] or when the osmolarity increases,[13, 14] there is a discharge of mucus from the goblet cells. In addition, sympathetic and parasympathetic nerves are located adjacent to conjunctival goblet cells, and sensory stimulation of the cornea causes goblet cell mucus discharge.[15, 16] All of these mechanisms can be thought of as protective, providing a way for the ocular surface to recognize foreign material, discharge mucus to trap it and, in association with aqueous tear secretion, remove it from the eye.

AQUEOUS LAYER AND LACRIMAL GLAND SECRETION

The aqueous portion of the tear film is formed primarily by the lacrimal gland and the accessory lacrimal glands of Krause and Wolfring. The main lacrimal gland is divided into orbital and palpebral portions by the levator aponeurosis and lies deep to the superotemporal fornix. The accessory glands of Krause lie mostly in the conjunctiva of the superotemporal fornix, with a few glands lying in the inferotemporal fornix. The glands of Wolfring are larger but fewer than the glands of Krause and lie in the conjunctiva approximately at the fornicial ends of the tarsal plates. A majority of the lacrimal gland fluid enters the fornices superotemporally.[17] From the fornices, lacrimal gland fluid travels, even in the absence of blinking, into the marginal tear strips. The distribution of this fluid in the marginal strips to the preocular film depends on the blink.[18]

The lacrimal gland is innervated by both parasympathetic and sympathetic nerves.[17] Parasympathetic fibers traveling with the lacrimal nerve stimulate lacrimal gland secretion.[19] Whereas β_1-adrenergic agonists also stimulate tear secretion,[20, 21] the role of sympathetic nerve fibers to the gland remains somewhat unresolved. Parasympathetic blockers and β_1-adrenergic blockers can diminish lacrimal gland secretion clinically.[21, 22]

The classical interpretation of the lacrimal secretory system has divided the system anatomically and functionally into two parts: (1) the basic secretors (goblet cells, accessory lacrimal glands, and oil glands) and (2) the reflex secretor (the main lacrimal gland).[23] More recently it has become clear that the main and accessory lacrimal glands routinely work simultaneously with one another.[24]

Main and accessory lacrimal gland secretion is regulated both centrally and peripherally. Centrally, parasympathetic nerves innervate lacrimal gland tissue, and their activity is modulated by sensory reflex arcs and emotion.[25] A large portion of tear secretion is dependent on the sensory reflex arc.[26] Jordan and Baum demonstrated that when the ocular surface was anesthetized with proparacaine hydrochloride, tear secretion, as determined by fluorophotometry, fell below physiologic baseline and decreased about 78%.[26] What is the basis for the residual tear secretion? It has been postulated that this remaining tear secretion is regulated peripherally by blood-borne neurohumoral agents, such as vasoactive intestinal peptide, that stimulate lacrimal gland secretory cells directly.[27]

The average tear flow in humans is about 1.2 μL/min and ranges between 0.5 and 2.2 μL/min.[26, 28] The volume of the tear fluid averages about 7 μL.[26, 28] About 1.1 μL of this total volume lies in the preocular film within the palpebral fissure, about 2.9 μL within the marginal strips, and about 4.5 μL within the fornices. Ehlers calculated the thickness of the precorneal tear film, based on quantitative data, to average about 7 to 9 μm. He demonstrated that the precorneal tear film is thickest—about 8.7 μm—immediately after blinking and gradually thins over a 30-second period to a thickness of about 4.5 μm.[29] The rate of thinning is fastest in the 5 seconds immediately after the blink. This thinning occurs too rapidly to be due to evaporation,[29] but it probably relates to the drainage of tears that commences on lid opening.[30]

The osmolarity of the normal human tear film averages 302 ± 6 (SD) mOsm/L.[31] Tear osmolarity seems to be the lowest in the morning after prolonged lid closure,[32] and to increase somewhat as the day progresses.[33] Besides the effects of evaporation on tear film osmolarity, the osmolarity of the lacrimal gland fluid itself actually increases with decreased rates of lacrimal gland secretion.[34]

The tear film has a unique electrolyte composition that differs from both aqueous humor and serum. The most notable but by no means the only difference in electrolyte composition is that of potassium. The potassium concentration averages about 23 mmol/L in the tear film,[35] about 5 mmol/L in the aqueous humor,[36] and 4.5 mmol/L in serum.[37] The electrolyte gradients between tears and serum and between tears and aqueous humor are maintained by the blood-tear and aqueous-tear barriers, and because of this the cornea and conjunctiva normally exist in a unique electrolyte milieu.

There are many different types of proteins in tear fluid, some of which come from the lacrimal gland, and others that leak into the tear film from the serum.[5] Relevant to this discussion is that the concentration of protein in lacrimal gland fluid decreases as the flow rate decreases.[38] In humans it has been shown that the concentration of lysozyme, a bacteriolytic protein, increases with increased tear secretion and decreases with decreased tear secretion.[39]

LIPID LAYER

The most superficial layer of the tear film is produced by the meibomian glands in the tarsal plate, which secrete sebaceous material at the mucocutaneous junction of the lid margin. Blinking compresses and stretches this secretion over the tear film to create and maintain the superficial oily layer. The glands of Zeis (sebaceous) and Moll (sweat) are located more anteriorly in the lid margin and are associated with the cilia.[17] The superficial oily layer has been estimated to be only 0.1 μm thick.[40] Its major role is to retard evaporation from the tear film. Indeed, in the rabbit, the evaporation rate of the tear film has been found to increase to four times baseline if the superficial lipid layer is removed.[41] In humans, the normal evaporative rate measures $4.07 \pm 0.40 \times 10^{-7}$ (SD) g/cm²/sec.[42]

BLINKING AND TEAR FILM STABILITY

The normal blink rate averages once every 5 seconds,[43, 44] and blinking is critically important in spreading freshly se-

creted lacrimal gland fluid.[18] In addition to lid movement, the globe movement that occurs relative to the lid with eye movement also plays a role in tear spreading. Most blinks are incomplete,[45] and eye movement probably compensates for this.

Just how stable is the tear film? Does the tear film rupture between blinks? Classic studies of tear film stability were performed by instilling fluorescein diluted with saline solution in the eye and watching for the appearance of dark spots through a cobalt blue filter. With this technique the normal tear film remained intact for over 10 seconds, with the film remaining stable for between 15 and 34 seconds in most normal eyes.[46] More recently it has been shown that the introduction of fluorescein and saline solution into the tear film decreases the stability of the tear film and that the tear film is actually more stable than previously recognized. Mengher and coworkers have studied tear film stability noninvasively by observing the image of a lighted grid reflected from its surface. In normal subjects, the stability of the tear film averaged about 40 seconds and ranged as high as 200 seconds. In 1% of normal subjects, the tear film ruptured before 6 seconds. In dry-eye patients, tear film stability averaged about 12 seconds, and in about two-thirds of them, tear film stability exceeded the normal 5-second interval between blinks.[47–49] The tear film, without the addition of eye drops, is a remarkably stable structure.

Pathology of Dry-Eye Disorders: The Ocular Surface

Although he did not have the benefit of electron microscopy, in many ways Sjögren's description of the ocular surface disease of KCS has never been surpassed.[1, 50–52] Morphologically, in KCS the conjunctiva is affected before the cornea. Initially, the conjunctival epithelium can appear normal,[1] but there is a loss of conjunctival goblet cells,[53, 54] and edema appears in the conjunctival stroma.[1, 55] As the disease becomes more advanced, fluid moves from the stroma to between the delicately attached conjunctival epithelial cells, and intercellular edema appears in the deeper layers of the conjunctival epithelium.[1, 55, 56] Later on, intracellular edema[50] appears and is manifested by decreased cytoplasmic density.[56] Conjunctival epithelial cells with decreased cytoplasmic density demonstrate blunting and loss of cell surface microplicae. As these membrane changes take place, discontinuities appear in the cell surface membrane.[53, 55, 56] As fluid moves between superficial conjunctival epithelial cells, there is an increase in conjunctival epithelial cell desquamation.[1, 55]

With time, and as the disease advances, there is gradually a squamous metaplasia of the conjunctiva,[57] with a further decrease in conjunctival goblet cell density[53, 58–60] and a subsequent increase in the surface area and flattening of conjunctival epithelial cells.[1] This change in epithelial cell shape is associated, first, with a decrease in nuclear size, followed by nuclear pyknosis, and ultimately, in later stages, by loss of cell nuclei.[59] As these epithelial changes take place, the intracellular, intercellular, and stromal edema disappear.[1]

Sjögren was the first to recognize that the severity of conjunctival disease varied with the topographic location.[50] He found that the conjunctival epithelial disease and goblet cell loss were more advanced within the palpebral fissure (within the bulbar conjunctiva left exposed by the lids) compared with bulbar conjunctiva covered by the lids, and that epithelial disease in exposed nasal conjunctiva was typically more advanced than disease in exposed temporal conjunctiva.[51] It has subsequently been shown by impression cytology that goblet cell loss in KCS is greater in the bulbar conjunctiva than in the palpebral conjunctiva[58] and greater in the nasal bulbar conjunctiva than in the temporal bulbar conjunctiva.

The cornea is more resistant than the conjunctiva to disease in KCS. Sjögren first noted that rose bengal would commonly stain the entire bulbar conjunctiva within the exposure zones, while staining only the inferior cornea.[1] In a rabbit model with surgically induced KCS, the earliest corneal morphologic changes consisted most notably of increased superficial cell desquamation and edema and followed morphologic changes in the conjunctiva by almost a year.[61] Lemp and colleagues studied the corneas of KCS patients in vivo with wide-field color specular microscopy and found a shift toward smaller superficial corneal epithelial cells in KCS.[62, 63] They interpreted this to reflect accelerated corneal desquamation in KCS.

What is the cause of these ocular surface changes? Sjögren concluded in 1933, based on his histologic observations, that in response to decreased lacrimal gland secretion there was a transudation of fluid through the conjunctiva.[50, 51] Balik suggested that the histologic changes could be explained by an increased osmotic gradient created across the conjunctiva by elevated tear film osmolarity.[64] About 20 years later, after multiple attempts, investigators finally demonstrated elevated tear film osmolarity in KCS.[31, 65] There is now considerable evidence to support the theory that elevated tear film osmolarity is the link between decreased tear secretion and ocular surface disease.[13, 14, 66, 67] The most powerful evidence is that which has been obtained by developing and studying rabbit models for dry-eye disease. In these rabbit models, the surface disease of KCS is dependent on and proportional to increases in tear film osmolarity and the duration of disease.[54, 55, 61, 68, 69]

Why do cells desquamate in the early stages of KCS, and why do the surface cells undergo a transformation (decrease in nuclear:cytoplasmic ratio) in the later stages of disease? To understand these phenomena it is crucial to understand the influence of water on desquamation.[70] This has been explored extensively with regard to the stratum corneum of skin, and there are some straightforward parallels. In the stratum corneum, cells are held together by ionic bonding created by negatively and positively charged groups on the proteins, glycoproteins, mucopolysaccharides, sterols, and lipid phosphatides found on the cell surfaces. The magnitude of the attraction varies directly with the magnitude of the charges and inversely with the distance between the two charges. Furthermore, the magnitude is affected by the dielectric constant of the material in the space between the cells. Water has a dielectric constant of 81 and damps ionic bonding 81 times as much as air with a dielectric constant of 1. In the early stages of KCS, intercellular edema, caused by the transudation of fluid across the conjunctiva, decreases ionic bonding between cells and results in increased cell desquamation. Later in the disease, the surface finally becomes desiccated, and this intercellular edema disappears. Now there is even less water and space than usual between

cells, and the intercellular ionic forces increase dramatically. It can be postulated that the flattened, enlarged cells with degenerating nuclei, which are seen in late KCS, are cells that under normal states of surface hydration are shed from the ocular surface.

It has been proposed that this squamous metaplasia or "skinlike" change in the ocular surface is a protective response that inhibits further fluid loss from the ocular tissues. Indeed, this is the case in the skin, where keratinized lamellae of stratum corneum form the major barrier against the loss of water and ions.[71]

Much thought has been devoted to factors other than osmolarity that may contribute to the surface disease of KCS. One of these factors is tear film breakup. Although about one-third of patients with dry eye develop discontinuities in their tear film in the interval between blinks, two-thirds do not.[47–49] In addition, although the average breakup time in patients with dry eye is significantly less than normal, most patients with dry eye do not experience tear film rupture between blinks. All this decreases the likelihood that decreased tear film stability causes the surface disease in KCS. How might tear film stability decrease as a *result* of the surface disease? Abdel-Khalek and associates reported a decrease in the number and height of conjunctival microplicae in KCS in humans, with a marked or total loss of cell surface microplicae with more advanced disease.[53] With these advanced changes in the cell surface membrane, we have observed in our rabbit models for KCS an apparently associated decrease in the cell surface glycoproteins. These cell surface glycoproteins form the glycocalyx that renders the ocular surface hydrophilic and, together with the microplicae on which they lie, bind the mucous layer of the tear film to the surface of the eye. As these cell surface specializations are lost, tear film stability decreases. Since these corneal changes occur late in the disease, we now recognize that dry spot formation is a late change in dry-eye disease. Clinically, any process that sufficiently damages the corneal epithelial cell surface accelerates the appearance of nonfluorescent spots within a fluorescein-stained tear film after the blink is withheld.

Another hypothesis that has received attention suggests that the changes that occur in the ocular surface are due not to the decrease in tear secretion but to an independent, parallel process that affects the ocular surface directly.[72–74] This appears highly unlikely given the many reports in the literature of KCS developing after surgical removal of the lacrimal gland.[24] Sjögren studied cases such as this and found that the ocular surface pathology was identical with that seen with autoimmune lacrimal gland disease.[1] It is simply not necessary to invoke a separate disease process, inflammatory or otherwise, unrelated to decreased tear secretion.

Mechanisms for Dry-Eye Disorders

It is helpful clinically to recognize that any condition that decreases tear secretion or increases tear film evaporation has the potential to increase tear film osmolarity and create the surface disease of KCS (Fig. 74–1).

DECREASED TEAR SECRETION

When tear secretion declines, several mechanisms increase tear film osmolarity. First, with decreased tear secretion, tear film turnover declines, permitting evaporation more time to concentrate the preocular tear film. Tear film turnover is a function of the rate of tear secretion. By fluorophotometrically monitoring the dilution in the tear film of a known amount and concentration of fluorescein dye, one can demonstrate that dye dilution and washout occur rapidly at high tear secretion rates. In contrast, dye is diluted less rapidly and retained in the tear film longer at low tear secretion rates. This slow dye dilution reflects decreased tear film turnover (Fig. 74–2).[28]

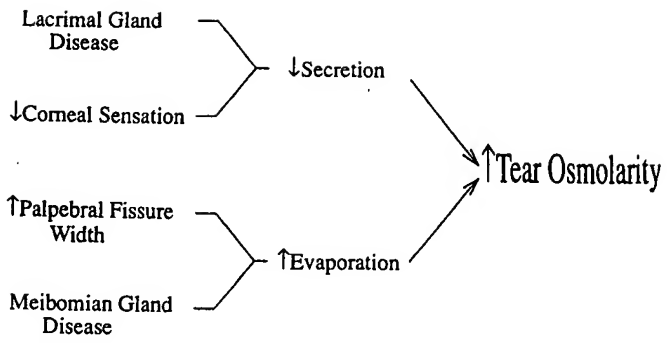

FIGURE 74–1. Mechanisms for elevated tear film osmolarity result in the surface disease of keratoconjunctivitis sicca (KCS).

Second, as tear secretion declines, the tear volume declines, but the interpalpebral surface area remains constant. The decrease in volume is about 25%.[75] Under these circum-

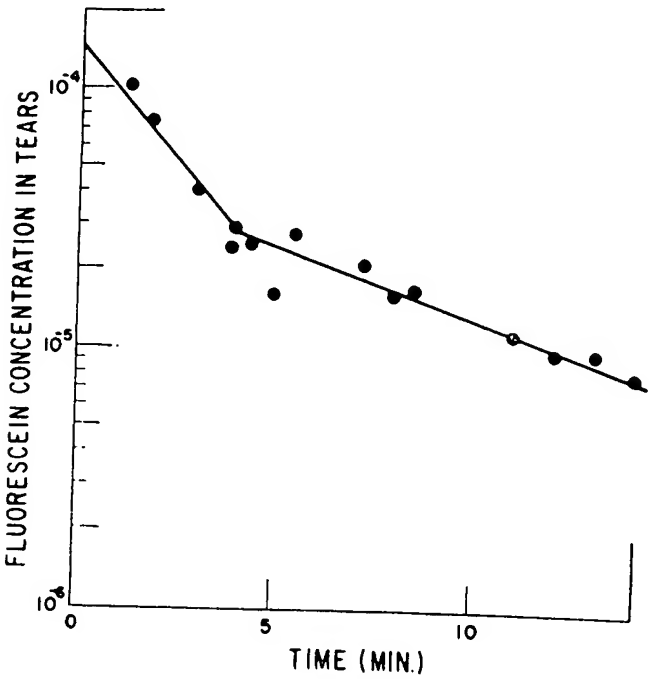

FIGURE 74–2. Fluorescein concentration in the tear film after fluorescein drop instillation. Sensory stimulation occurring with drop instillation increases the rate of tear flow and dye dilution observed initially. With lower flow rates, dye dilution slows, illustrating that with decreased tear secretion tear film turnover declines. With tear fluid remaining in the eye longer, evaporation has more time to concentrate the preocular tear film. (From Mishima S, Gasset A, Klyce SD, Baum JL: Determination of tear volume and tear flow. Invest Ophthalmol 5:264, 1966.)

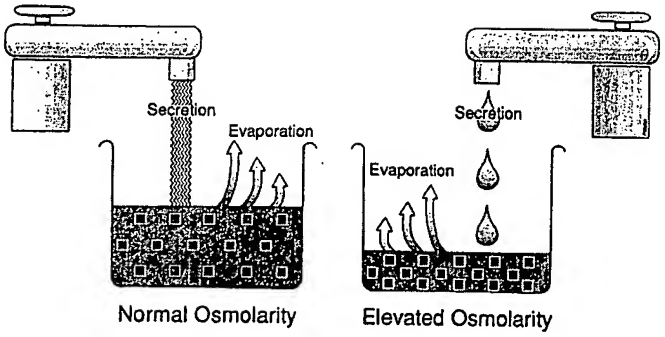

FIGURE 74–3. With decreased tear volume, tear film evaporation has a greater effect on tear film osmolarity.

stances, tear film evaporation has a greater effect on tear film osmolarity (Fig. 74–3).

Finally, the lacrimal gland fluid osmolarity increases as the secretory rate declines, independent of the effects of evaporation.[34] This has been demonstrated in rabbits, and there is now evidence that such a mechanism is also operative in humans (Fig. 74–4).[35]

LACRIMAL GLAND DISEASE

The most significant anatomic cause of lacrimal gland dysfunction is damage from an autoimmune mechanism. Dry-eye disease from this mechanism is called KCS. Patients with KCS and dry mouth (xerostomia) are said to have *primary Sjögren's syndrome* or *sicca syndrome*, whereas patients with these problems along with rheumatoid arthritis, systemic lupus erythematosus, or scleroderma are said to have *secondary Sjögren's syndrome*.[76] Histologically, lacrimal gland tissue from these patients is indistinguishable, and it shows mononuclear cell infiltration with lymphocytes, some lymph follicle formation, plasma cells, atrophy of gland parenchyma, and fibrosis.[50, 77, 78] Patients with primary Sjögren's syndrome are more likely to have anti-La (SS-B) antibodies, lack antibodies to salivary gland ducts, and have a high frequency of histocompatibility antigen HLA-DR3.[79, 80] Patients with secondary Sjögren's syndrome have a high frequency of HLA-DR4 and are salivary duct antibody–positive.[80] Immunocytochemical studies have shown the mononuclear cell infiltrates to contain primarily B cells and Leu-3–positive helper T cells.[81] The actual mechanism by which these inflammatory cells destroy lacrimal gland tissue, thus decreasing aqueous tear secretion, is unknown.

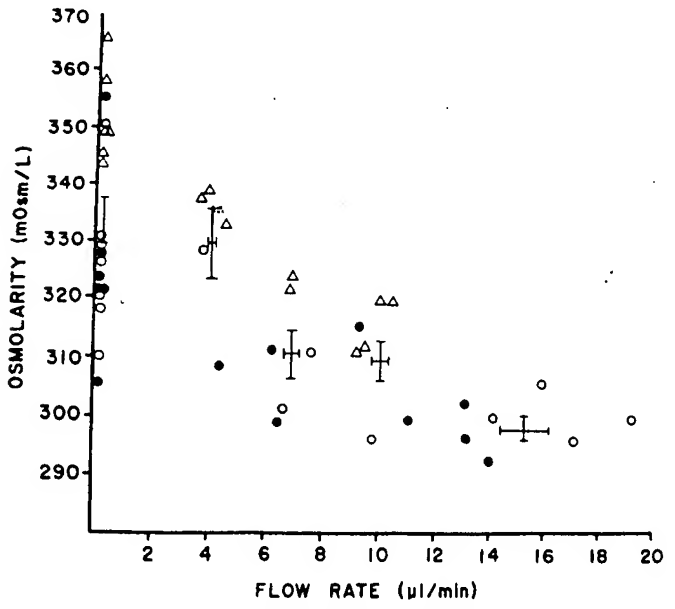

FIGURE 74–4. Lacrimal gland fluid osmolarity as a function of the flow rate. Osmolarity increases as the flow rate declines independent of the effects of evaporation. *Closed* and *open circles* and *open triangles* represent data from separate rabbits; *vertical* and *horizontal crossbars* represent the mean ± standard error of the mean for lacrimal gland fluid osmolarity and flow rate, respectively. (From Gilbard JP, Dartt DA: Changes in rabbit lacrimal gland fluid osmolarity with flow rate. Invest Ophthalmol Vis Sci 23:804, 1982.)

It is important to keep in mind that any inflammatory or cicatrizing ocular surface disease has the potential to decrease aqueous tear secretion by closing off the lacrimal gland excretory ducts and damaging the accessory lacrimal glands. These disorders would include ocular cicatricial pemphigoid, Stevens-Johnson syndrome, and severe chemical burns. Clearly, surgical removal of lacrimal gland tissue is also a cause for decreased tear secretion.

DECREASED CORNEAL SENSATION

Schimmelpfennig and Beuerman showed in rabbits that *unilateral* lesions of the trigeminal ganglion, which abolish corneal sensation in one eye, do not diminish the blink rate.[82] In contrast, Collins and associates have shown that *bilateral* corneal anesthesia induced by topical proparacaine decreases the blink rate about 30%, to an average rate of 17.2 blinks/min.[83] In 22% of their subjects, the blink rate did not decrease after proparacaine treatment. Since freshly secreted tears are spread from the marginal tear strips to the interpalpebral ocular surface only by movement of the lids, and since the stability of the tear film is finite, the phenomenon of a decreased blink rate after bilateral corneal anesthesia can attain clinical significance in selected patients.

Although bilateral corneal anesthesia is necessary to see an effect on the blink rate, neurotrophic keratitis clearly develops with unilateral loss of corneal sensation. A unilateral decrease in corneal sensation appears to be related to the development of surface disease in two ways. First, intact corneal sensation partially drives tear secretion, and with a decrease in corneal sensation there is a decrease in tear secretion.[26] Topical proparacaine treatment causes a transient 60 to 75% decrease in tear secretion. It has been demonstrated that this decrease in tear secretion can increase tear film osmolarity in the presence of normal lacrimal gland tissue.[84] Neurotrophic keratitis is, in part, a dry-eye disorder, and studies have noted that, like eyes in KCS, these eyes show abnormal rose bengal staining, decreased conjunctival goblet cell density, decreased corneal epithelial glycogen, and conjunctival epithelial cell abnormalities.[69]

There are, however, changes in the cornea that cannot be accounted for merely by decreased tear secretion or increased tear osmolarity. Among these changes are significant decreases in corneal mitosis and thickness that are not reversed by lid closure,[85, 86] and corneal morphologic and biochemical changes that are beyond what can be accounted for by changes in osmolarity alone. The trigeminal nerve

FIGURE 74–5. Increased surface area for evaporation is evident in this patient with thyroid eye disease.

exerts an independent trophic influence on the cornea that may occur via axonally transported neurotransmitters and neuropeptides.[87] There is evidence for such an effect in multiple systems,[88] and it appears that an analogous mechanism plays a role in the corneal changes of neurotrophic keratitis. Specifically, in neurotrophic keratitis there is a decrease in corneal acetylcholine, substance P, and calcitonin gene–related peptide. There is good evidence that these substances stimulate cell mitosis, and their loss, along with decreased corneal glycogen, probably plays a significant role in the decreased corneal mitosis and healing problems seen in this condition.[89]

INCREASED TEAR FILM EVAPORATION

Increased rates of evaporation from the tear film can increase tear film osmolarity and create dry-eye disease independent of abnormalities of aqueous tear secretion. Evaporation can increase secondary to increased palpebral fissure width or meibomian gland dysfunction. Patients with dry-eye disease from increased tear film evaporation complain of symptoms virtually identical to those of patients with dry-eye disease from decreased tear secretion.

LARGE PALPEBRAL FISSURE WIDTHS

Eighty-seven percent of normal adults have palpebral fissure widths of 10 mm or less, and the majority of palpebral fissures average less than 9 mm in width.[90] The palpebral fissure width is important in the understanding of dry-eye disorders because tear film evaporation is proportional, in part, to the ocular surface area exposed.[91]

The palpebral fissure width may be large for no reason other than heredity, or it may be enlarged after lid surgery or in association with thyroid eye disease (Fig. 74–5). In patients with thyroid eye disease it has been possible to correlate increased palpebral fissure width with both elevated tear film osmolarity and ocular surface disease evidenced by rose bengal staining.[92]

MEIBOMIAN GLAND DYSFUNCTION

Meibomian gland dysfunction results as a sequel to or in association with meibomitis. In patients with meibomian gland dysfunction there is stenosis or closure of the meibomian gland orifices.[93] The natural history of meibomitis and meibomian gland dysfunction appears to involve the progressive stenosis and then closure of the meibomian gland orifice (Fig. 74–6). Mishima and Maurice studied the effect of meibomian gland orifice closure on corneal thickness and

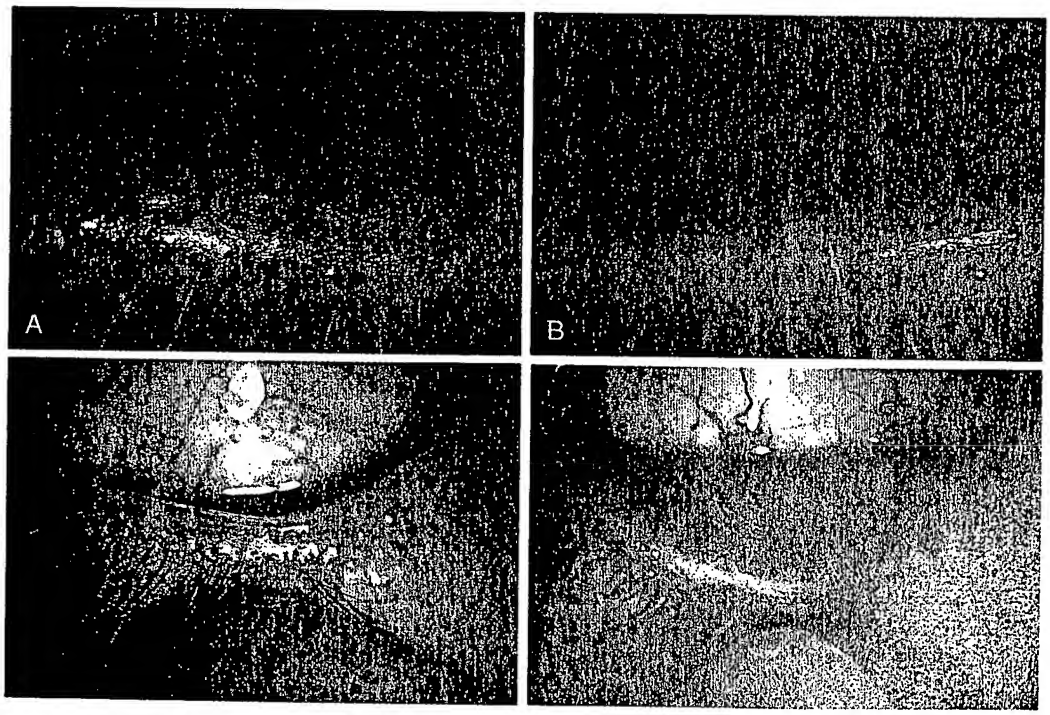

FIGURE 74–6. In the normal lid margin *(A)*, meibomian gland orifices are visible and the margin is free of blood vessels. The normal meibomian gland "piano-key" pattern is visible beneath the tarsal conjunctiva when the lid is pulled down *(B)*. With meibomian gland orifice stenosis, the orifice is no longer visible, but oil can be expressed when pressure is applied to the lid *(C)*. With meibomian gland orifice closure, the orifice is no longer visible and oil cannot be expressed *(D)*. There is distortion and obliteration of the normal meibomian gland piano-key pattern beneath the tarsal conjunctiva.

concluded that closure increases tear film evaporation.[94] More recently, it has been shown that closure of meibomian gland orifices in the presence of normal lacrimal gland tissue results in an increase in tear film osmolarity[68, 95] and in the development of the ocular surface disease elements of KCS.[68]

The blockage at the meibomian gland orifice causes a retention of oil within the meibomian gland, and the meibomian gland duct becomes dilated. The stasis of oil within the gland results in an inflammatory response in and around the gland, and eventually this inflammation spills over to involve the ocular surface. *Meibomitis* refers to the inflammatory component of this disease and *meibomian gland dysfunction* to the lipid deficiency that develops as gland anatomy is altered by chronic inflammation. There is a possibility that, in some patients, meibomitis may create sufficient conjunctival inflammation to decrease tear secretion by damaging accessory lacrimal gland tissue in the conjunctiva.[68] This is an interesting possibility that needs further exploration.

Differential Diagnosis of Ocular Irritation and Dry-Eye Disorders

The patient complaining of chronic eye irritation can have any one of many causes for the ocular discomfort. The problem is not merely one of determining whether there is dry-eye disease or not. The physician must first determine a differential diagnosis for the patient's discomfort and then narrow this list to a specific diagnosis or diagnoses. Often a dry-eye disorder is the culprit, but frequently there are other causes. It is important to determine the basis for the symptoms because, as is discussed later, therapy varies.

HISTORY

A good history is one of the most important tools that an ophthalmologist has to reach a diagnosis in a patient who complains of chronic eye irritation. Seven questions need to be answered to extract the most information from a patient.

1. *Character.* What does the irritation feel like? Is it a sandy-gritty feeling, burning, foreign body sensation, or increased "awareness" of the eyes? Do the eyes itch?
2. *Location.* Where is the irritation located? Is it on the surface of the eye, in the eye, on the lid margin, or on the skin?
3. *Diurnal variation.* Are the symptoms worse at any particular time of day? Are they worse on awakening or late in the day? Are they worse on awakening and in the evening, with some attenuation of symptoms in the middle of the day?
4. *Onset.* Did the symptoms start suddenly, or did they develop gradually? Do symptoms occur in clearly delineated episodes or is this a continuous problem?
5. *Duration.* How long have the symptoms been present?
6. *Aggravating factors.* Is there anything that makes the symptoms worse—wind, smoke, low humidity (i.e., airplane cabins), reading, watching TV, contact lens wear, artificial tears?
7. *Alleviating factors.* Is there anything that makes the symptoms better—hot compresses, eye closure, high humidity, artificial tears?

Keratoconjunctivitis Sicca

Patients with KCS most commonly complain of a sandy-gritty feeling in their eyes that is worse as the day progresses. Symptoms increase as the day proceeds because of the evaporation that takes place during the day with the eyes open. After an evening of sleep with eye closure, symptoms characteristically diminish. The symptoms are insidious in onset, and initially patients may only complain of an increased awareness of their eyes. Late in the disease symptoms may be present throughout the day, but usually the diurnal variation persists. As the cornea becomes involved, patients develop sensitivity to light. Ninety percent of patients with Sjögren's syndrome are women, and older than 40 years.[76, 96, 97]

Meibomitis and Meibomian Gland Dysfunction

Patients with meibomitis also complain of chronic sandy-gritty irritation (or burning) in their eyes, but in these patients the symptoms are worse on awakening in the morning. Tear secretion decreases at night during sleep, the eyelids are next to the cornea, and inflammatory mediators have an opportunity to accumulate and act on the surface of the eye. Patients also frequently complain of redness of their eyes in the morning. Some patients complain of symptom exacerbation with reading. The symptoms are insidious in onset. Some patients may have discovered that hot compresses provide some relief.

With time, meibomian gland inflammation causes gland damage, and meibomian gland dysfunction develops. Tear film evaporation then increases, and these patients develop a second peak in their symptoms late in the day. Finally, after several years, the meibomian gland inflammation resolves as gland architecture is destroyed and heals with scarring. These patients then experience a resolution of their early morning symptoms but a progression of their symptoms late in the day. In severe cases, patients can be symptomatic throughout the day, but again, as in advanced KCS, the diurnal variation usually persists.

Occasionally, patients with meibomian gland dysfunction and orifice closure complain of watery eyes. This is probably from the loss of the meibomian lipid barrier at the lid margin that normally acts as a barrier to the aqueous tears and from the loss of the lipid layer that normally decreases surface tension, thus holding the tear film tight to the globe.

Anterior Blepharitis

Patients with anterior blepharitis have symptoms at the anterior lid margin. Specifically, patients have crusting or experience irritation at the base of the lashes. The adjacent lid skin may be involved. Later in the disease, there can be loss of lashes. There is no diurnal variation, and the onset is usually insidious.

Large Palpebral Fissure Width

The symptoms in patients with large palpebral fissure width are nearly identical to those of patients with lacrimal gland disease. Sandy-gritty feelings and burning become worse as the day progresses. Because lacrimal gland function is normal in these cases, patients can notice excess tearing.

Decreased Corneal Sensation

A history of fifth-nerve trauma or surgery is usually key in patients with decreased corneal sensation. It is important to recognize, however, that there are many other causes of decreased corneal sensation, any one of which may play a role in the dry-eye disease of a specific patient (Table 74–1). Remember that any condition that decreases corneal sensation decreases tear secretion and may increase tear film osmolarity.

One of the less frequently recognized syndromes is the dry-eye condition, associated with elevated tear film osmolarity, that may develop after long-term contact lens wear, particularly long-term hard contact lens wear.[98, 99] Contact lens wear decreases corneal sensation, and the effect is more pronounced with hard contact lenses and extended-wear soft contact lenses.[100, 101] The effect is cumulative, and it is not uncommon to see patients who have worn hard lenses for longer than 15 years develop lens intolerance requiring discontinuation of lens wear. Many of these patients complain of dryness and sandy-gritty feelings in their eyes that become worse as the day goes on even in the absence of contact lens wear. For this reason, it is important to ask about contact lens wear in patients who complain of eye irritation.

Once the contact lens history is positive, and if contact lens wear continues, it is important to determine whether there are any features of the contact lens cleaning and sterilization system (i.e., preservatives) or contact lens fit that may be contributing to ocular irritation.

Medicamentosa

Ocular irritation due at least in part to eye drop use should be suspected in all patients using traditional artificial tears more than four times a day. These patients generally give a history of regular and frequently escalating eye drop use. Both preserved and nonpreserved solutions can be responsible, although there is now one commercially available preservative-free solution that appears to be free of this side effect.[12, 102–104] In these cases, complaints of stinging with eye drop use should raise suspicions. Patients with medicamentosa characteristically are unable to describe a diurnal pattern to their symptoms—symptoms are equivalent throughout the day. This is because the damage is promoted by continued overuse of topical medications, even though the use of these medications may temporarily mask symptoms by increasing the lubrication of the ocular surface.

TABLE 74–1. **Major Causes of Decreased Corneal Sensation**

Neurotrophic keratitis (damage to the fifth nerve)
Corneal surgery
Limbal incisions
Penetrating keratoplasty
Lamellar keratoplasty
Radial keratotomy
Excimer laser surgery
Herpes simplex
Topical medications
β-Blockers
Atropine
Diabetes
Contact lens wear
Aging

Lacrimal Drainage Obstruction

The most likely basis for symptoms of tearing and tear overflow is lacrimal drainage obstruction. Some patients may complain of irritation of the skin at the lateral canthus rather than frank tearing. The skin here can become "chapped" from repeated exposure to tear fluid. Symptoms from lacrimal drainage obstruction are insidious in onset and are usually exacerbated by exposure to wind and environmental irritants.

Allergic Conjunctivitis

Patients with allergic conjunctivitis complain of ocular itching. They may also complain of increased mucus production by the eye. The onset is commonly seasonal and may be associated with exacerbation of hay fever, asthma, or eczema.

Nocturnal Lagophthalmos

Nocturnal lagophthalmos patients commonly complain of burning in the eyes that is worse on awakening. There is frequently a history of previous lid surgery or thyroid eye disease.

Superior Limbic Keratoconjunctivitis

Patients with superior limbic keratoconjunctivitis complain of burning and irritation and develop symptoms and remissions somewhat abruptly. A diurnal pattern to the symptoms is not usually evident. The factors initiating the development of exacerbations and remissions are not known. Episodes may last from days to years, and remissions may last for weeks or may be permanent. Vision is not affected. Women are affected more frequently than men, and it is common to see a history of thyroid dysfunction.

Superficial Punctate Keratitis (Thygeson's)

Thygeson's superficial punctate keratitis is characterized by the insidious onset of photophobia, irritation, and decreased vision. The course of the disease is episodic and lasts about 2 to 3 years. The cornea shows elevated punctate staining with fluorescein.

Dry Eyelid Skin

Some patients say their "eyes" feel dry but when questioned carefully reveal that they are referring to their eyelid skin. This common ambiguity underlines the need to determine the location of the symptoms. Frequently these patients report the daily use of soap on the skin around their eyes.

Tarsal Foreign Body

Patients with a chronic foreign body sensation may have a tarsal foreign body. Symptoms are frequently monocular. In addition to exogenous material, a meibomian gland–derived conjunctival concretion (or concretions) can form the basis for symptoms that can remain enigmatic for years.

Mucus-Fishing Syndrome

Some patients with ocular irritation develop the practice of reaching into their conjunctival cul-de-sac with their fingers and "fishing" out the mucus strand that they find there. These patients complain of eye irritation and increased mucus production by the eye. Conjunctival trauma induces an additional increase in mucus production, and a vicious circle follows. Traumatized areas stain with rose bengal, and the condition resolves once the patient's behavior is altered.[105]

Blepharospasm

Patients with primary blepharospasm may complain of a "tired feeling" in the eyes that is actually their interpretation or description of their difficulty keeping their eyes open. On careful questioning, it becomes apparent that there is actually no eye irritation but rather an involuntary closure of the eyes or an inability to keep the eyes open. Driving, reading, and exposure to sunlight may exacerbate these symptoms. Since dry-eye symptoms are commonly exacerbated by the same factors, it is very important to keep this frequently missed diagnosis in mind.

In patients with secondary blepharospasm there is underlying chronic eye irritation. Failure of the patient to respond to dry-eye treatment may highlight the presence of this second condition.

Nonspecific Ocular Irritation

Not all ocular irritation is caused by eye disease. The eye may be normal, and environmental irritants, such as smoke and chemicals, may be responsible for the symptoms.

Normal Eyes With Hypochondriasis

Normal eyes with hypochondriasis is a relatively uncommon problem. Usually ocular irritation is due to one or more of the entities previously mentioned. Nevertheless, it is important to recognize patients without organic disease, and sometimes a careful history, which in turn fails to mesh with the examination, can provide the first clue.

EXAMINATION

In this section we focus on the key signs of KCS, meibomitis and meibomian gland dysfunction, and anterior blepharitis, because these disorders are frequently the most difficult to distinguish from one another.

Keratoconjunctivitis Sicca

In early disease, the ocular surface and tear film can appear normal (Fig. 74–7). Perhaps the earliest change seen on slit-lamp examination is an apparent increase in the viscosity of the tear film. This is observed as a slowing of the surface flow of the tear film just after the lid is elevated with a blink. After a wet fluorescein strip is applied to the inferior tarsal conjunctiva and the patient is given the opportunity to blink a couple of times, the ophthalmologist will note that in patients with decreased tear volume, the fluorescein remains dark and does not fluoresce. In very early disease, the inferior marginal tear strips may fluoresce temporally but not nasally. (Fluorescein eye drops, such as the type that contains an anesthetic, spoil the ability to observe these and other tear film changes helpful in the evaluation of the patient with chronic eye irritation.) As the disease progresses and there is a further decrease in tear production, decreased tear volume becomes apparent, mostly as a decrease in tear meniscus volume, and debris appears in the tear film. In late disease, the decrease in tear volume becomes apparent over the conjunctiva and manifests itself as a decreased luster of the bulbar conjunctiva (Fig. 74–8).

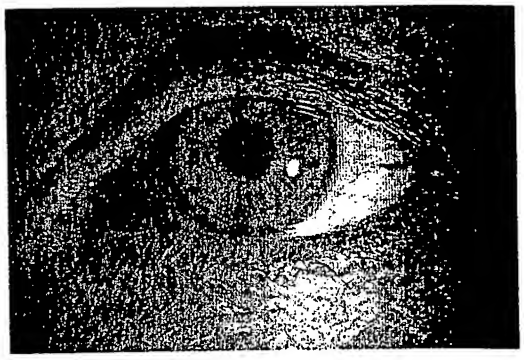

FIGURE 74–7. A patient with early keratoconjunctivitis sicca (KCS). The tear film appears normal before the instillation of dyes. The diagnosis of KCS was based on a sandy-gritty irritation that was worse toward the end of the day, rose bengal staining of the nasal bulbar conjunctiva within the exposure zone, and elevated tear film osmolarity.

Meibomitis and Meibomian Gland Dysfunction

The patient should be examined for facial telangiectasias, especially on the bridge of the nose and cheeks, which suggest acne rosacea, a skin condition associated with meibomitis. At the slit lamp look first for lid margin telangiectasias, and then examine the meibomian gland orifices (Fig. 74–9). Normally the meibomian gland orifices are visible as a series of round openings in the lid margin. As meibomitis develops and meibomian gland dysfunction sets in, "stenosis" of the meibomian gland orifices can be seen. With stenosis, the meibomian gland orifice cannot be seen on slit-lamp examination; however, when pressure is applied to the lid

FIGURE 74–8. A patient with late keratoconjunctivitis sicca (KCS). A healed corneal perforation is evident inferiorly within the palpebral fissure. Many patients with late KCS develop a ptosis such as that seen in this patient.

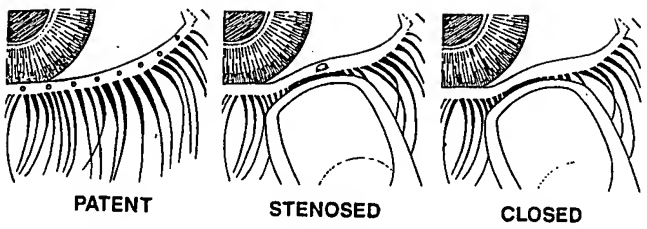

FIGURE 74–9. Meibomian gland dysfunction can be graded by examining the meibomian gland orifice. Patent orifices first become stenosed and then close.

margin, oil can be expressed through the stenosed opening. At this stage, it is common to see bloating of the meibomian glands beneath the inferior tarsal conjunctiva, along with meibomian cyst formation, and injection of the inferior tarsal conjunctiva. As oil is lost from the surface layer of the tear film, the tear film takes on a watery appearance that is especially apparent with fluorescein in the tear film. As the disease progresses, inflammation brings in new fibrous tissue and the lid margin becomes thickened and blunted. Closure of meibomian gland orifices develops—the meibomian gland orifices cannot be seen, and when pressure is applied to the lid margin oil cannot be expressed. Eventually the meibomian gland pattern is obliterated, and the inflammatory component of the disease burns itself out. Along with a loss of the tear film oil pattern, there is frequently increased vascularity of the bulbar conjunctiva with inferonasal vascular encroachment on the cornea. These vascular changes represent, in the late stages, not active inflammation but an anatomic change after long-standing inflammation.

It is helpful to recognize that patients with large palpebral fissure widths are more susceptible to symptoms from meibomian gland dysfunction than are patients with smaller palpebral fissure widths. The large surface area of the tear film associated with large palpebral fissure widths puts an evaporative stress on the tear film,[91] and a relatively small amount of meibomian gland dysfunction can make these patients symptomatic. Patients with large palpebral fissure widths are also more sensitive to decreases in tear secretion for the same reason.

Anterior Blepharitis

The examination of the eyelashes and anterior lid margin is key. Patients with seborrheic disease show inflammatory changes or flaking of the skin at the base of the lashes. This is essentially a process analogous to dandruff of the scalp. Purulent material is seen with bacterial disease. With eczema, dry roughened skin may be observed involving the eyelid skin. Unlike meibomitis or posterior blepharitis, the meibomian glands and tarsal conjunctiva are not primarily affected. If inflammation of the lashes continues, eventually loss of lashes may be observed.

DIAGNOSTIC TESTING

The usefulness of a diagnostic test is determined in large part by its sensitivity and specificity. *Sensitivity* refers to positivity in the presence of disease, and *specificity* refers to negativity in the absence of disease.[106]

Schirmer Test

The Schirmer test involves folding sterile filter paper strips and inserting them between the lower lid and the globe at the lateral one-third of the lid margin. The result is expressed as millimeters of wetting at 5 minutes. If proparacaine is instilled in the eye before performing this test, it is known as the basic Schirmer test.

Lamberts and coworkers found that 15% of normal subjects had basic Schirmer test results of 3 mm or less.[107] Twenty-eight percent of normal men and 20% of normal women had basic Schirmer test results of 5.5 mm or less. In a separate series, again using the basic Schirmer test, only 17% of KCS eyes had basic Schirmer test results of 3 mm or less, and only 26% of KCS eyes had a result of 5.5 mm or less.[108] False-negative and false-positive results appear to be a considerable problem with the basic Schirmer test.

False-positive results appear to be reduced somewhat if the test is performed without proparacaine. This is quite logical, since the decreased corneal sensation from proparacaine decreases tear secretion in all eyes. In separate series, performing the Schirmer test without proparacaine and using 3 mm or less of wetting as the cutoff, false-positive results were no higher than 10%. Nevertheless, sensitivity was still poor and ranged between 10 and 25%. Many patients with dry-eye disease had false-negative results.[109, 110]

Although false-positive results were no higher than 10%, it is easy to see that if the test were to be done on a general population containing patients with and without disease, and if the prevalence of dry-eye disease was about 10% of this population, roughly 75 to 90% of the subjects who tested positive would be false-positive results. The conclusion is that the physician must not rely solely on Schirmer test results to rule dry-eye disease in or out.

Because so much attention has been given to the Schirmer test, and because, intuitively, one would expect its predictive value to be greater than the studies indicate, it is worthwhile to examine why its accuracy is so disappointing.

There are several factors that confound its accuracy. First, the Schirmer test, whether done with proparacaine or without, does not measure physiologic tear flow. Even when done with proparacaine, the tear secretion rate calculated from Schirmer strip wetting exceeds the physiologic tear flow by a factor of about 15.[26]

Perhaps more important than this is evidence that suggests that the Schirmer test may be influenced by two conflicting factors. The first, decreased tear production, would decrease Schirmer test results while it contributes to elevated tear osmolarity. The second, however, decreased meibum production from meibomian gland dysfunction, would increase Schirmer test results even though it contributes to elevated tear osmolarity, dry-eye surface disease, and dry-eye symptoms. Under normal circumstances, oil on the lid margin acts as a barrier to aqueous tears. We have previously postulated that oil on the lid margin, and oil absorbed from the lid margin onto the Schirmer strip, retards aqueous tear absorption on the Schirmer strip. Patients with dry eye from meibomian gland dysfunction could therefore have false-negative Schirmer test results due to facilitation of water absorption by the filter paper.[68] This would contribute to the poor sensitivity of the Schirmer test in selecting which patients have dry eye based on symptoms,[42]

increased tear film osmolarity,[108] and ocular surface disease.[111]

Rose Bengal

It turns out that all ocular surface epithelium would stain with rose bengal were it not for the blocking effect of attached mucus.[112, 113] Based on our studies of a rabbit model for KCS, it appears that staining in human patients depends on loss of cell surface glycoproteins that normally contribute to the glycocalyx and enable the mucous layer to attach to the ocular surface. This occurs after goblet cell loss but relatively early in the conjunctiva; the corneal epithelium loses cell surface glycoproteins much later in the natural history of the disease. Goblet cell loss alone does not appear to be sufficient for rose bengal staining.[61]

Rose bengal staining is best performed by instilling a relatively large drop of the dye in the unanesthetized eye and then rinsing the excess out of the eye with an eyewash or irrigating solution. If an insufficient volume of dye is placed in the eye, staining may be missed. Anesthetic should not be used because this decreases reflex tearing and seems to increase the discomfort ultimately associated with dye use in eyes with ocular surface disease.

Van Bijsterveld developed a scoring system for rose bengal dye that divides the ocular surface into three zones: nasal bulbar conjunctiva, cornea, and temporal bulbar conjunctiva.[111] Each zone is given a score ranging from zero to 3, with zero indicating no staining and 3 indicating essentially confluent staining. Scores for each eye are totaled, and in any eye, scores of 3.5 or greater are, according to this system, taken to indicate a positive test for KCS. The van Bijsterveld scoring system has proved invaluable in clinical studies and as a tool in quantitatively following KCS patients.

Such a scoring system, however, can give false-negative results in dry-eye patients with mild disease. In one study, 49% of the patients with dry eye had rose bengal staining scores of less than 3.5.[109] Furthermore, a purely quantitative score does not provide any of the information that the clinician can obtain from careful observation of the rose bengal staining pattern. Since most ocular surface disease associated with ocular irritation may be associated with rose bengal staining, and not all such surface disease is due to dry eye, a quantitatively positive test does not necessarily indicate lacrimal gland disease. The test provides not only useful information on the presence or absence of KCS but also information that can be used to narrow the differential diagnosis of the patient with chronic ocular irritation.

What follows is a description of the natural history of rose bengal staining, both intensity and pattern, in several ocular surface diseases. The diseases reviewed are those that are particularly relevant in the evaluation of the patient with chronic ocular irritation.

Keratoconjunctivitis Sicca

In KCS resulting from lacrimal gland dysfunction, the conjunctiva stains more than the cornea. In early disease, staining may be absent or may be limited to the nasal bulbar conjunctiva within the exposure zone. In moderate disease, there is staining of the nasal and temporal bulbar conjunctiva within the exposure zones, and the nasal staining is usually greater than the temporal staining (Fig. 74–10). Later in the disease, there is staining of the inferior cornea within the exposure zone, and as the disease progresses, the stain rises higher on the cornea (Fig. 74–11).

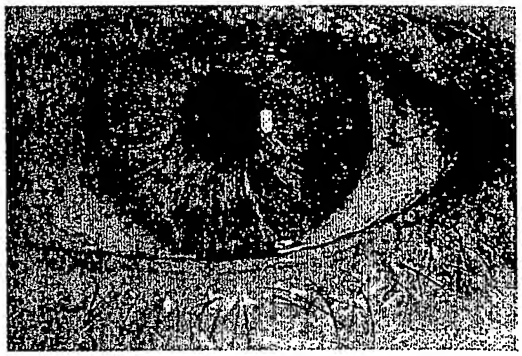

FIGURE 74–10. Rose bengal staining typical for moderate KCS. The conjunctiva stains more than the cornea, and the nasal conjunctiva stains more than the temporal conjunctiva.

Meibomitis and Meibomian Gland Dysfunction

Meibomitis precedes meibomian gland dysfunction, and initially, there can be either no rose bengal staining or staining of the inferior or superior bulbar conjunctiva under the eyelids and outside the exposure zones. With more severe inflammation, staining spreads and affects the cornea at least as much as the conjunctiva within the exposure zone. Staining in late disease, with the presence of advanced meibomian gland dysfunction, can appear very similar to staining in late KCS. With advanced meibomian gland disease, however, in contrast to late KCS, the tear volume appears normal (Fig. 74–12).

Nocturnal Lagophthalmos

In nocturnal lagophthalmos, rose bengal stains the inferonasal corneal and conjunctival epithelium and there is usually a discrete line of demarcation between stained and unstained tissue (Fig. 74–13).

Superior Limbic Keratoconjunctivitis

In superior limbic keratoconjunctivitis, rose bengal stains the superior bulbar conjunctiva and the superior cornea (see Fig. 74–13).

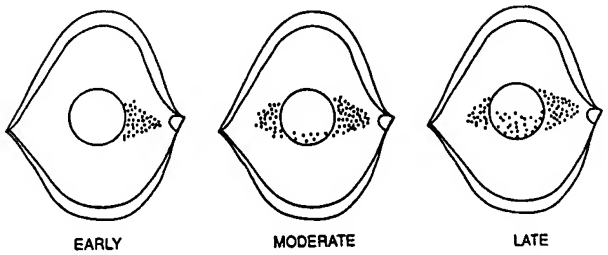

FIGURE 74–11. Rose bengal staining in early, moderate, and late keratoconjunctivitis sicca.

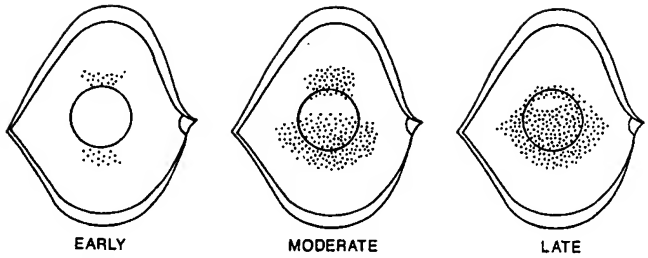

FIGURE 74–12. Rose bengal staining in early, moderate, and late meibomitis and meibomian gland dysfunction. Early in the disease, inflammation predominates, whereas late in the disease dry-eye disease predominates. As inflammation resolves (with treatment or disease progression), staining of the inferior and superior bulbar conjunctiva clears. Dry-eye disease in these patients is based on increased tear film evaporation from a deficient tear film lipid layer.

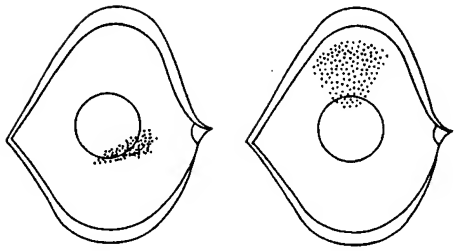

FIGURE 74–13. Rose bengal staining in lagophthalmos *(left)* and superior limbic keratoconjunctivitis *(right)*.

Tear Osmolarity

The tear samples for tear osmolarity measurements are collected with either hand-drawn micropipettes or 0.2-μL microcaps. These pipettes enable the physician to collect about 0.1 to 0.2 μL of fluid from the inferior marginal tear strip by capillary action without stimulating the ocular surface.[31] The patient is positioned for slit-lamp examination, and the light beam is rotated to a horizontal position. The light is kept on the lower lid and raised to the inferior tear strip just as the patient is asked to look up and the sample is collected.

Tear osmolarity measurement can be performed directly, or the tear sample can be transferred into a column of water-saturated Cargilles B immersion oil for storage. If the sample is to be stored overnight, the open end of the storage tube is sealed with parafilm.[114]

The ease with which tear osmolarity measurements can be performed has improved dramatically with the introduction of the Advanced Nanoliter Osmometer (Model 3000, Advanced Instruments, Inc., Norwood, MA). Both this new instrument and the original Clifton nanoliter osmometer measure tear osmolarity by freezing-point depression (Fig. 74–14).[92] However, the new instrument does not require a water supply and has the advantages of requiring standardization only every 1 to 2 weeks, simpler sample loading and unloading, easier measurement performance, and lower cost. Since the instrument remains standardized, measurements can be performed while the patient is in the office. Measurement takes about 12 minutes but requires less attention than

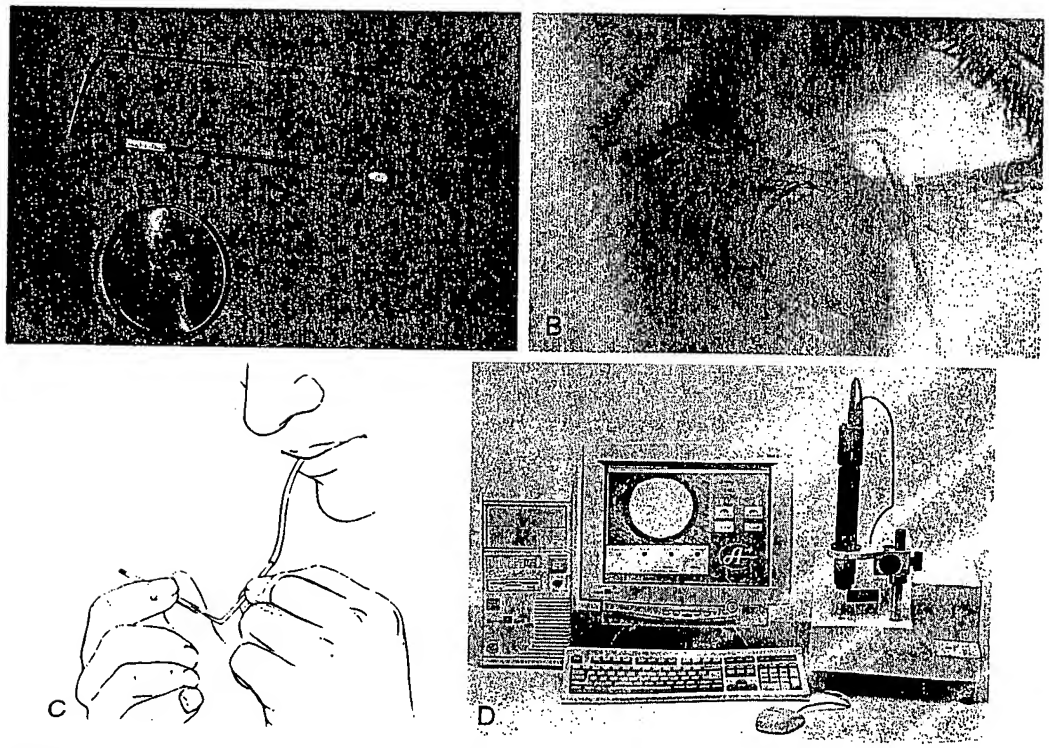

FIGURE 74–14. Method of tear osmolarity measurement. An L-shaped tear collection pipette and tear storage tube *(A)* provide a method of collecting tear fluid without reflex tearing or sample evaporation. Tear fluid is collected from the inferior marginal tear strip *(B)* and then may be stored in the oil-containing storage tube *(C)* or may be loaded directly into the Advanced Nanoliter Osmometer. *(D)*. (*A*, From Gilbard JP, Farris RL, Santamaria J: Osmolarity of tear microvolumes in keratoconjunctivitis sicca. Arch Ophthalmol 96:677, 1978. Copyright 1978, American Medical Association.)

that because an alarm beeps when the sample is ready to be examined. Tear osmolarity is now a test that can be done in the office.

Given the central role of elevated tear film osmolarity in the pathogenesis of the ocular surface disease of KCS, it comes as no surprise that tear osmolarity measurement is the most sensitive and specific diagnostic test for dry eye. In the first published study, using a reference value or cutoff of 312 mOsm/L, the sensitivity of a positive measurement was 94.7% and the specificity was 93.7%.[31] In a more recent study, the sensitivity was 90% and the specificity 95%.[110]

Clearly, elevated tear film osmolarity does not necessarily indicate the presence of autoimmune lacrimal gland disease. It indicates an imbalance between the rate of tear secretion and the rate of evaporation in which a decrease in the former or an increase in the latter, or both, is sufficient to overwhelm the homeostatic mechanisms that normally keep tear osmolarity near 302 mOsm/L. Although 312 mOsm/L has been used as a reference value for disease, values of 310 and 311 are consistent with the presence of early dry-eye disease, and we no longer consider results in this range to be truly normal.

There are probably two mechanisms for false-negative results. The first is reflex tear secretion at the time of sample collection. Once proficiency is obtained in collecting samples, this problem seems rare. The second mechanism is based on the observation that in extremely severe disease or in the presence of ocular surface inflammation, tear film osmolarity can be in the normal range. We believe that this is due to a breakdown in the blood-tear barrier in these patients that results in tear osmolarity coming into an osmotic equilibrium with plasma. Fortunately, in these patients, disease is so advanced that diagnosis can almost always be made on the basis of history and examination alone, with or without rose bengal staining.

Lactoferrin

In the early 1980s, Stuchell and colleagues measured lactoferrin levels in dry-eye patients and normal controls using rocket electrophoresis and reported some interesting findings.[39] In their study, tear samples were collected in one of two ways, both of them without anesthetic. The first technique involved touching a small (2 × 6 mm) piece of filter paper to the inferior bulbar conjunctiva for 5 seconds, and the second involved inserting a Schirmer strip for 5 minutes.[98] They called the tear fluid collected the first way *basal tears*, and the fluid collected with a Schirmer strip *reflex tears*. In basal tears, lactoferrin levels averaged 154 ± 82 mg/dL in KCS patients and 137 ± 102 mg/dL in normal persons, and this difference was not significant. In reflex tears, however, the lactoferrin level was significantly lower in KCS patients compared with normal persons (171 ± 69 mg/dL versus 327 ± 187 mg/dL, respectively). This measurement of lactoferrin levels in reflex tears had a sensitivity of 54% and a specificity of 94%.[109]

It is known that the concentration of protein in lacrimal gland fluid normally increases as the flow rate increases.[38] It can be postulated that when tear secretion is stimulated, normal patients attain higher flow rates than those of patients with lacrimal gland disease. As a result of the lower stimulated tear secretory rates in patients with lacrimal gland disease, lactoferrin concentrations generally do not climb to levels reached in normal persons. At unstimulated low flow rates, there is no significant difference in lactoferrin concentration between patients with and without disease.

The measurement of tear lactoferrin levels subsequently evolved into an office test called Lactoplate, a commercially available radial immunodiffusion assay. With forceps, a sterile 4-mm filter paper disc is placed in the inferior fornix, without the use of anesthetic, for 5 minutes. The disc is then removed, excess fluid is blotted off, and the disc is placed in a reagent gel chamber. The chamber is sealed tightly and left at room temperature for 72 hours. The diameter of the antigen-antibody precipitation ring is measured in millimeters and converted to milligrams per deciliter based on a supplied conversion table. The reference value is 90 mg/dL.

In a study by Lucca and associates comparing Lactoplate results in dry-eye patients with those in normal age-matched controls,[110] the results paralleled those obtained by Stuchell and colleagues[39] using rocket electrophoresis and measuring lactoferrin levels in basal rather than in reflex tears. Lactoferrin ranges and medians were virtually identical in dry eyes and normal eyes. The test had a sensitivity of only 35% and a specificity of 70%.

The Lactoplate measurement took 3 days and was subsequently replaced by the LactoCard solid-phase enzyme-linked immunosorbent assay that takes 10 to 15 minutes (Touch Scientific, West Chester, PA). In the multicenter study, sensitivity, or positivity in the presence of KCS, was 0% for mild KCS, 26.3% for moderate KCS, and 83.3% for severe KCS. For patients in whom a diagnostic test is most needed, the sensitivity is less than a flip of a coin. Specificity, or negativity in the absence of disease, was 98.9%.[115]

History, examination, rose bengal staining, and tear osmolarity measurement are the most useful methods for developing a differential diagnosis. These methods form a good basis for therapy using the staged approach detailed later.

Treatment of Ocular Irritation and Dry-Eye Disorders

It has been commonly taught that dry-eye treatment begins with lubricating eye drops, also known as *artificial tears*. Attempting to treat dry-eye patients with lubricant solutions is frequently a frustrating experience. Dissatisfaction with the results of treatment has been attributed to the effect of preservatives or the short retention time of these drops in the eye. The toxicity of preservatives has been well documented.[116–118]

In fact, until recently, the efficacy of traditional artificial tear solutions has been limited by an additional important mechanism. In order to understand this additional mechanism, it is necessary to review what is known about ophthalmic solutions and the electrolyte requirements of the surface of the eye.

ELECTROLYTES AND THE OCULAR SURFACE EPITHELIUM

To some extent, progress in our understanding of ophthalmic solutions and the surface of the eye parallels the understand-

ing of intraocular irrigating solutions and the corneal endothelium. In 1960, Merrill and coworkers reported that 0.9% (isotonic) sodium chloride solution was toxic to conjunctival epithelium in tissue culture.[119] Solutions that had a more complete ionic composition did not show the same toxicity. Nine years later, in 1969, Sussman and Friedman showed that frequent instillation of 0.9% sodium chloride solution into normal rabbit eyes led to hyperemia and photophobia and eventually to corneal epithelial breakdown.[104] This work was largely ignored until 1985, when Bachman and Wilson studied desquamation from rabbit corneas.[120] They found that corneal desquamation was increased with exposure to 0.9% sodium chloride solution in comparison with a solution also containing potassium, bicarbonate, calcium, magnesium, and phosphate. These data were later corroborated with morphologic studies.[121] In 1986, Fullard and Wilson demonstrated increased desquamation in vivo in human corneas using clinically relevant 30-second exposure times.[122]

What emerges clearly from all this work is that the cornea and conjunctiva have electrolyte requirements that are not met by solutions containing only sodium and chloride. Ultimately it was shown that the electrolyte requirements of the surface of the eye coincide with the unique electrolyte balance of the normal tear film. Specifically, the maintenance of normal conjunctival goblet cell density and corneal glycogen levels depends on the unique electrolyte balance of the tear film. As pointed out earlier, this electrolyte balance is different from that of both aqueous humor and serum. Of key importance are the levels of sodium, chloride, potassium, and bicarbonate and, to a lesser extent, the presence of trace amounts of calcium, magnesium, and phosphate.[12, 35, 123] Without the proper electrolyte content and balance, a lubricating eye drop has the potential to cause both epithelial toxicity and aggravation of goblet cell loss, a clinical syndrome known as medicamentosa.[12, 102, 103] As we select and use lubricating eye drops, it is important to keep these principles in mind.

PHASE 1: ARTIFICIAL TEARS AND TREATMENT OF ASSOCIATED CONDITIONS

Modification of eye drop use, hot compresses, lid massage, lid hygiene, and systemic tetracycline therapy are all therapeutic options that can be exercised at the time of the first visit, when the history, examination, and diagnostic testing indicate their potential usefulness. After 3 months, after repeat patient evaluation, consideration is given to implementation of the second phase of treatment. In cases of obvious and severe aqueous tear deficiency where corneal ulceration is a concern, the interval between phase 1 and phase 2 is compressed, but patients such as this are unusual.

Artificial Tears

Since elevated tear film osmolarity causes the surface changes in dry-eye disease, the first goal of treatment with artificial tear solutions is to lower the elevated tear film osmolarity. When an isotonic or even a weakly hypotonic eye drop is placed in a dry eye, the tear film osmolarity remains elevated, continuing to osmotically pull water out of the surface of the eye even though the surface is wet. In order for an artificial tear solution to effectively lower elevated tear osmolarity, it needs an osmolarity of about 170 mOsm/L.[124] An eye drop with such osmolarity takes tear film osmolarity from about 330 mOsm/L in a dry eye to about 285 mOsm/L and in doing so, flips the osmotic gradient between the tear film and eye surface so that water can move in to rehydrate the dehydrated tissues. A new treatment called TheraTears (Advanced Vision Research, Woburn, MA) is the first treatment that is hypotonic, and it has been shown, with q.i.d. dosing, to produce sustained lowering of elevated tear film osmolarity with continued treatment.[125] In addition, TheraTears precisely matches the electrolyte balance of the human tear film.[12, 35, 123] By lowering elevated tear film osmolarity and providing this electrolyte balance, TheraTears has been shown in preclinical studies to restore both conjunctival goblet cells and corneal glycogen levels in dry-eye disease (Fig. 74–15).[125] Widespread clinical use of TheraTears is now confirming its clinical efficacy, and this solution appears to have a unique primary role in the treatment of dry-eye disorders.

Medicamentosa Treatment

It is likely that loss of conjunctival goblet cells reduces the lubricity and comfort of the eye surface. Preservatives and eye drops that alter or distort the normal electrolyte balance of the tear film have the potential to reduce goblet cell density and cause medicamentosa (see Fig. 74–15). The symptoms of medicamentosa reflect changes to the ocular surface that take weeks to months to fully heal, and these surface changes, not merely the presence of foreign fluid in the tear film, account for the symptoms. Most patients with medicamentosa do not complain of irritation immediately after drop instillation. The lubricating properties of these solutions can symptomatically decrease discomfort temporarily not only from the surface disease of dry eye but also from the changes produced by these solutions themselves. Adding to the protean nature of medicamentosa is that the fluorescein and rose bengal staining patterns in these eyes can appear essentially identical to those of meibomitis.

Since the surface diseases of medicamentosa, KCS, and meibomitis can coexist, the best way to eliminate medicamentosa as a factor is to discontinue all traditional lubricating eye drops and nonessential topical medications for 3 months. We know from animal experiments that normal conjunctiva requires 2 months to fully recover from injury,[54] and we believe this 3-month period gives the surface of these diseased eyes time to recover to a new plateau. We use this principle repeatedly in managing patients with ocular surface irritation: Therapeutic maneuvers designed to improve the health of the surface should be given about 3 months to observe their maximal effect.

Hot Compresses

Hot compresses are indicated in patients with meibomitis or meibomian gland dysfunction. We instruct patients to place a clean washcloth under hot water and then apply it to closed lids for about 30 to 60 seconds while massaging both upper and lower lids with their fingertips. We recommend that patients perform this procedure two to four times a day, and if desired, the procedure can be performed even more frequently.

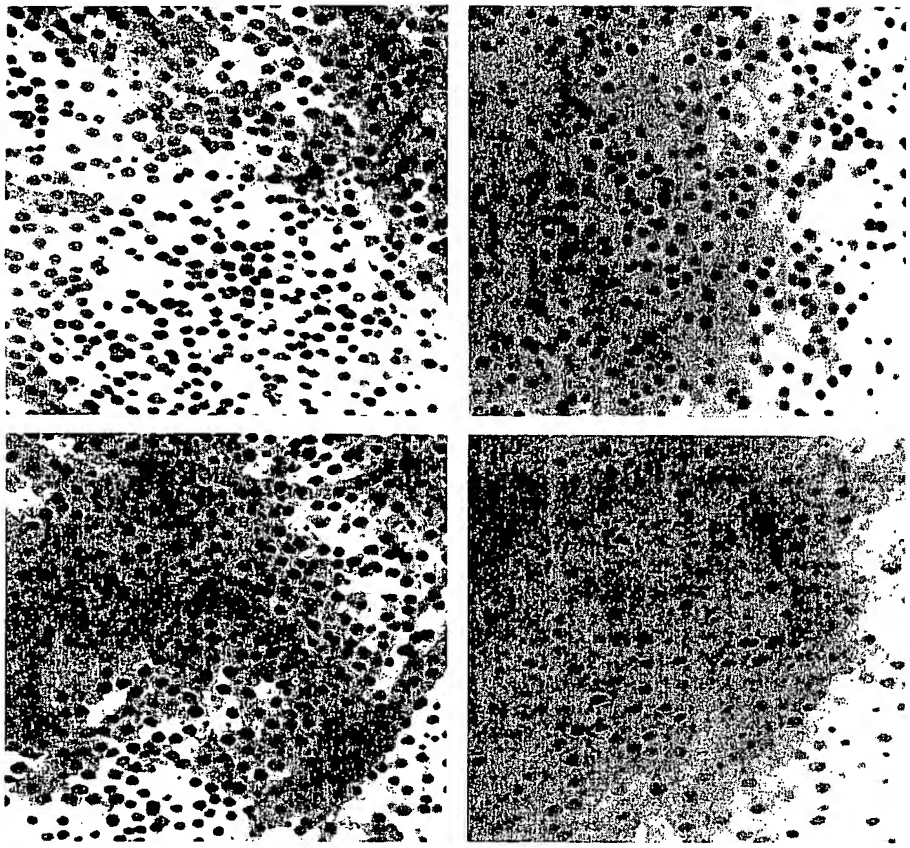

FIGURE 74–15. Conjunctival flat mounts show restoration of goblet cells in TheraTears–treated dry eyes *(lower left)* approaching normal controls *(upper left)*, and significantly better than untreated dry eyes *(upper right)*. Dry eyes treated with a traditional lubricating eye drop *(lower right)* show a significant loss of goblet cells versus untreated dry eyes *(upper right)*. (From Gilbard JP, Rossi SR: An electrolyte-based solution that increases corneal glycogen and conjunctival goblet-cell density in a rabbit model for keratoconjunctivitis sicca. Ophthalmology 99:600, 1992.)

Hot compresses probably have two mechanisms of action. First, the heat decreases inflammation by increasing the blood supply to the lids. Second, the massaging action combined with heat helps express lipid into the tear film, bolstering the lipid layer and decreasing stasis of lipid in the meibomian gland. Retention of lipid within the meibomian gland may be a stimulus for inflammation.[68] Hot compresses are useful, then, in treating both meibomitis and meibomian gland dysfunction, a helpful feature because these conditions are usually associated with one another. There are no known side effects associated with this treatment if it is performed properly. Patients obviously should be careful not to burn the skin of their eyelids.

Lid Hygiene

Lid hygiene is reserved for patients with flaking and irritation of the skin at the base of the lashes due to a dandruff-like process. This problem clinically responds to washing with dilute shampoos. We instruct patients to place a small amount of dandruff shampoo in the palm of a hand and to mix it with water, working up a lather. This cleans the hands and dilutes the shampoo. Once the soap is diluted and only suds remain, the fingertips are used to shampoo the base of the eyelashes. Residual soap is washed away with a moistened washcloth. The procedure can be performed at a sink, but it is most easily performed in a shower. The procedure is performed daily until flaking resolves and resumed when flaking returns. There are other ways of shampooing the eyelashes, but the technique described spares the patient complicated quantitative dilution formulas, the need for cotton swabs, and the risk of poking the cornea with swabs that are more difficult to manipulate than the patient's own fingertips.

Tetracycline

It is widely recognized that systemically administered tetracycline is useful in treating posterior blepharitis or meibomitis with or without ocular rosacea.[126–131] In addition to their antibacterial properties, tetracyclines inhibit collagenase activity[132–134] and decrease leukocyte chemotaxis[135–138] and phagocytosis.[139] We believe it is through these antiinflammatory properties that systemically administered tetracycline exerts its therapeutic effect on meibomitis.

Patients with meibomitis are usually started on 250 mg of tetracycline twice a day, in conjunction with the use of hot compresses. Patients remain on this dose for 3 months and are then reevaluated. Patients with meibomitis experience an improvement or resolution of their early morning symptoms. On examination a decrease in tarsal and bulbar inflammation can be observed, along with a decrease in ocular surface staining. If the patient has responded, the dose is reduced by half, and the patient is continued on this new dose for another 3 months. The dose is titrated every 3 months, such that the patient is on the minimal dose necessary to control morning symptoms. If the patient is essentially symptom free on 250 mg twice weekly, an attempt is made to discontinue the medication. Some patients require treatment indefinitely, and others can be successfully tapered off the medication. It should be remembered that tetracyclines are contraindicated in pregnant or nursing women.

Patients with gastric complaints from tetracycline may sometimes tolerate doxycycline (50 mg/day). Minocycline (100 mg/day) is also effective and rarely causes the dermal photosensitivity that is seen with other tetracyclines.

PHASE 2: ADDITIONAL MEASURES TO LOWER ELEVATED TEAR OSMOLARITY

The second phase of therapy continues treatments that have been effective in the first phase and adds additional treatments as necessary to control elevated tear film osmolarity and rehydrate the tear film and ocular surface.

Punctal Occlusion

William Beetham introduced the use of punctal occlusion as a treatment for dry eye in 1935.[140] Beetham described the use of electrocautery and presented data showing that this procedure reduced ocular surface disease as indicated by staining. Subsequent studies performed in the 1980s confirmed his findings.[141, 142] Dohlman hypothesized that punctal occlusion is helpful for dry eye by decreasing elevated film osmolarity,[143] and Gilbard and associates later demonstrated that punctal occlusion decreases elevated tear film osmolarity in dry-eye patients (see Fig. 74–15).[67, 144]

Punctal occlusion probably decreases tear film osmolarity by increasing the tear volume. With increased tear volume, evaporation has less of an effect on tear film osmolarity. Furthermore, freshly secreted tear fluid may have more of a dilutional effect on the tear film in the presence of decreased tear drainage.[67]

Punctal occlusion is helpful for those dry-eye disorders characterized by elevated tear film osmolarity, whatever the cause. We find three criteria useful in determining which patients will benefit from punctal occlusion. Patients must satisfy two of these three criteria to qualify for permanent punctal occlusion: (1) sandy-gritty irritation that becomes worse as the day progresses; (2) a rose bengal staining pattern characteristic of aqueous tear deficiency; and (3) elevated tear film osmolarity. An exception is made for patients with neurotrophic keratitis.[145] Since corneal sensation is lost or absent, and tear osmolarity may be normal owing to increased corneal permeability,[69] epithelial staining is our sole criterion for punctal occlusion in these patients.

In addition to decreasing tear film osmolarity, punctal occlusion also increases the tear film volume. So there is a second group of patients who may benefit from punctal occlusion. These are patients with incomplete lid closure, such as those who have incomplete lid closure after blepharoplasty, who develop physical desiccation of the inferior cornea. In these patients punctal occlusion increases the height of the inferior marginal tear strip, and this enlarged strip can better spread tear fluid over the inferior cornea in the absence of full excursions of the upper lid. This effect seems to be independent of the effect of punctal occlusion on tear osmolarity.

Although punctal occlusion has been shown to reduce elevated osmolarity and rose bengal staining, punctal occlusion has been shown, in controlled studies, to have no effect on decreased goblet cell density.[142] Why? In our studies of tear osmolarity and electrolytes in patients with lacrimal gland disease, we found there was an increase in tear osmolarity and an increase in all measured tear electrolytes.[35] There was, however, a significantly disproportionate increase in tear sodium levels in these patients. In earlier studies we had demonstrated that disproportionately high sodium levels depleted mucus-containing conjunctival goblet cell density.[12] Although punctal occlusion can add water to the tear film, it cannot correct the goblet cell–depleting disproportionate increase in tear sodium levels seen in KCS. For this reason, we continue TheraTears treatment in patients after punctal closure.

There are several ways to close puncta "permanently," and it is helpful to divide these into *reversible* and *irreversible* groups.

Reversible

Freeman was the first to develop a series of silicone punctal plugs for reversible punctal occlusion. These plugs are now produced by several companies each of which produce them in a range of sizes. As plugs become smaller, they become easier to insert, but also easier to lose in the canaliculus. As plugs become bigger, they become harder to insert. I have been most satisfied with plug sizes in the middle of the existing commercial ranges. This size is usually called "small." All these plugs consist of a dome portion that sits on the surface of the lid, a middle shaft portion that sits within the distal canaliculus, and an arrowhead–shaped tip that is positioned deeper in the canaliculus and helps keep the plug in place.

First-generation punctal plugs frequently fell out, and when they were in, patients said they could feel them on extremes of gaze. The current generation of punctal plugs has addressed these problems. To reduce extrusion, some vendors have increased the diameter of the arrowhead–shaped tip. One of these vendors has also added tapering to the shaft portion of the plug. Another vendor has produced softer silicone in order to reduce the extrusion forces generated from eyelid rubbing. To reduce symptoms from the dome portion of the plug, all vendors have flattened the dome, two have reduced its diameter, and a third has tilted the dome so that it lies more flush with the lid margin. As the dome diameter decreases, it becomes easier to lose a plug in the canaliculus.

The procedure is most easily performed with the patient in the recumbent position and with +3.00 readers or weak loupes. For placement of inferior plugs, the patient is instructed to tuck the chin to his or her chest and to look up and away from the punctum, and for superior plugs, to point the chin toward the ceiling and to look down and away from the punctum. The punctum is held away from the globe by using the thumb to hold the lid against the orbital rim. With a nondisposable punctal dilator held with a short cotton-tipped applicator, the aim is to dilate the punctum without rupturing the punctal sphincter, and then to dry the punctal orifice quickly. While the thumb continues to hold the lid in position away from the globe, the dilator and cotton-tipped applicator are put aside, and the punctal inserter, loaded with the plug, is used to insert the plug. It can be helpful to catch the open punctum with the lateral edge of the plug tip and to rotate the plug into position. Patients can expect minor irritation in the nasal corner of the eye that subsides in a day or so.

There has been commercialization of a "temporary reversible" technique that involves transiently closing the punctum with collagen rods or suture fragments. The technique's usefulness is limited to that of a diagnostic trial.

Irreversible

Cauterization is used to attempt permanent and irreversible closure of the punctum. As punctal plugs have improved, the role of cauterization has decreased. I have largely abandoned cauterization in favor of punctal plugs. There is value in being able to open a punctum that has previously been closed.

Cauterization may be done at the slit lamp or with the aid of magnifying loupes. An injection of lidocaine is given in the region of the punctum. After confirmation of anesthesia, a low-temperature (two-battery) cautery is inserted into the distal canaliculus and turned on for 1.5 to 2 seconds. The instrument is then withdrawn from the punctum. It is helpful to compress the wire loop on the cautery tip before use. This narrows the loop and permits the distal canaliculus and punctum to close better in response to the heat.

Usually the inferior puncta are closed first, and if necessary based on the persistence of symptoms, the superior puncta are closed later. We usually wait at least 8 weeks, and preferably 3 months, before proceeding with closure of the superior puncta. Again, this interval gives the ocular surface time to heal. Closure of the inferior puncta alone decreases tear film osmolarity, and a further decrease is seen after closure of the superior puncta (Fig. 74–16).[67]

It is important to recognize two features of both punctal plug insertion and punctal cautery. Although both procedures seek to close the punctum permanently, puncta may open spontaneously after both procedures. Two separate studies have found a 22% extrusion rate after punctal plug insertion, albeit these studies were performed with first-generation plugs.[67, 142] The new plug designs may have a lower rate of extrusion. An earlier study had found that 25% of cauterized puncta reopened.[141] Furthermore, although the closure of a punctum with a silicone plug is meant to be a reversible procedure, the closure may become irreversible via the migration of the plug into the canaliculus or by an anatomic closure of the drainage system from scarring stimulated by plug insertion.

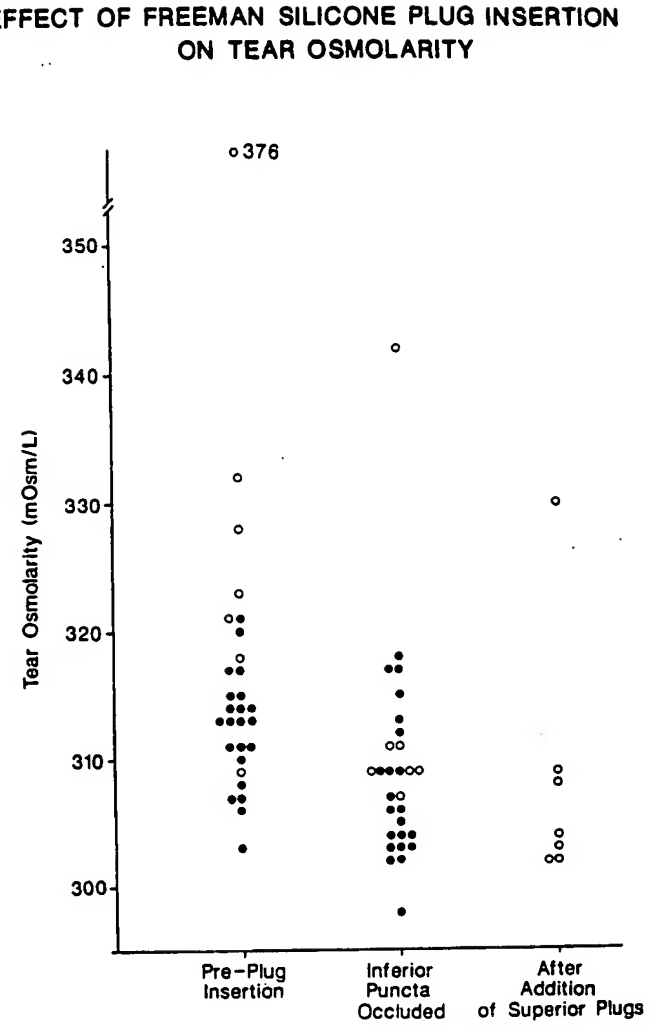

FIGURE 74–16. Punctal occlusion decreases tear film osmolarity, and closure of the upper and lower puncta decreases tear film osmolarity more than closure of the lower punctum alone. *Open circles* represent eyes that ultimately received inferior and superior plugs; *solid circles*, eyes that received inferior plugs alone. (From Gilbard JP, Rossi SR, Azar DT, et al: Effect of punctal occlusion by Freeman silicone plug insertion on tear osmolarity in dry eye disorders. CLAO J 15:216, 1989.)

Ointments

Ointments can be a useful adjunct in the treatment of dry eye. The major mechanism of action of these ointments may be based on their ability to coat the eye surface and tear film, retarding evaporation. The daytime use of these ointments may be particularly helpful in patients with meibomian gland dysfunction as well as those patients with incomplete lid closure. In patients with complete eye closure, we find no usefulness or rationale for the use of these ointments at night before sleep. In patients with incomplete eye closure, they are helpful before sleep and may be used with or without lid taping, depending on the severity of the lid closure abnormality.

Humidifiers and Moist Chambers

The lower the ambient humidity, the higher the rate of tear film evaporation. Conversely, the higher the ambient humidity, the lower the rate of tear film evaporation. The ability of high ambient humidity to retard evaporation, and thus help control tear osmolarity, can be exploited for therapeutic effect by increasing room humidity with humidifiers or by increasing local humidity with moist chamber spectacles. Humidifiers are particularly practical for patients who spend a large portion of their time in one or two locations (i.e., home and office). To maximize the effectiveness of moist chamber spectacles, the device should contact the face and be airtight. Unfortunately, although effectiveness increases with a tight fit, discomfort from pressure on the face increases.[146–148]

The subjective improvement observed in dry-eye patients after a good night's sleep represents the therapeutic moist chamber effect created by lid closure. Dry-eye patients who are exposed to extremes of low humidity for limited periods (i.e., airline cabins for several hours) can benefit from simple eye closure during these times of evaporative stress.

Low-water-content contact lenses may function like moist chambers, blocking evaporation from the underlying cornea. Unfortunately, there is a high risk of sight-threatening complications associated with their use.[149] We do not recommend currently available contact lenses as a treatment for dry eye.

A scleral lens made of a modern gas-permeable material has been described and is a very effective moist chamber.[150] These lenses appear to have a role in desperate cases where there has been a failure to maintain corneal epithelial integrity using other means.

Tarsorrhaphy

Many patients with severe dry-eye disease develop a protective ptosis. Perhaps this develops because these patients have a tendency to rub their eyes. A smaller palpebral fissure width decreases the evaporative stress on the tear film and ocular surface.

Tarsorrhaphy decreases interpalpebral surface area surgically and is used as a last resort in severe dry-eye disease, usually in the context of a persistent epithelial defect or corneal ulceration. Our clinical impression is that tarsorrhaphy is more effective therapy than pressure patching in such cases, perhaps because of better oxygen delivery to the ocular surface.

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